

Practitioner's Docket No. 701586-052522-US***PATENT*****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: Waxman, et al.

Confirm. No.: 1019

Application No.: 10/509,533

Group: 1633

Filed: May 26, 2005

Examiner: NGUYEN, Quang

For: METHOD OF USING ANTI-APOPTOTIC FACTORS IN GENE EXPRESSION

DECLARATION BY DR. DAVID WAXMAN

I, David Waxman, Ph.D., declare as follows:

1. I am a Professor of Cell and Molecular Biology in the Department of Biology at Boston University, and I am a Professor of Medicine in the Department of Medicine at Boston University School of Medicine.
2. A true copy of my curriculum vitae is attached herewith.
3. For the past almost three decades my research has concentrated in studying the responses in mammals to the challenges imposed by exposure to drugs and other xenochemicals. My research has elucidated the function of a large number of genes which encode cytochrome P450 enzymes that catalyze oxygenation of lipophilic foreign compounds. Expression of these P450 genes is controlled by a complex array of molecular regulatory circuits that respond to varying physiological conditions and changes in environmental stimuli.
4. I am a co-inventor of the above-identified patent application.
5. I have been advised that the Examiner has cited International Patent Publication No. WO 99/05299 to Waxman et al. ("Waxman"), International Patent Publication No. WO 99/55382 to

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Bilbao et al. ("Bilbao"), U.S. Patent No. 6,709,866 to Robertson et al. ("Robertson") and an article by Beidler et al. ("Beidler"), in the Office Action dated August 8, 2007.

6. I have been advised that the Examiner has stated that a person skilled in the art would have combined Bilbao, Robertson and Beidler with Waxman to come up with the method of my invention.

7. I have been asked to provide my opinion regarding the Examiner's conclusions based on Waxman in combination with Bilbao, Robertson and Beidler.

8. I disagree with the Examiner for the following reasons.

9. I am a co-inventor of Waxman.

10. Waxman is specifically directed to methods of killing neoplastic cells using NADPH-cytochrome P450 reductase (RED) gene transfer in combination with cytochrome P450 gene transfer to enhance the sensitivity of tumor cells to anti-cancer drugs that are activated by P450 enzymes.

11. The Examiner stated that Waxman describes that the method can be combined with "other established cancer therapeutic genes, including tumor suppressor genes, such as p53; apoptotic factors, such as bax, tumor necrosis factor alpha, and caspases; and cytokines, such as interleukin 2, interleukin 4, and interleukin 12." (Page 12, lines 3-9).

12. My present invention requires transducing the cell with an apoptosis inhibiting agent. Whereas none of the above-listed molecules prevent apoptosis.

13. Apoptosis is a process of programmed cell death. Thus, if one wishes to kill a cell, such as a cancer cell, one would think of apoptotic, i.e., apoptosis inducing factors.

14. One way of killing the cells described in Waxman, is to start apoptosis, i.e., use apoptosis inducing factors. This is the complete opposite of agents that would prevent cell death, i.e. an

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apoptosis **inhibiting** agent. Accordingly, it makes sense that the Waxman publication does not list any apoptosis inhibiting agents.

15. Based on the goal of cancer treatment, using an agent that would prevent cell death, i.e. be anti-apoptotic, would be counterintuitive.

16. Bilbao is not directed to treatment methods for cancer, neither is Robertson or Beidler.

17. I am not aware of any established cancer treatment methods prior to the filing of the present application that taught or suggested using anti-apoptotic agents or preventing cell death in combination with a cancer therapy.

18. Therefore, not only would there not have been any motivation to combine Waxman with Bilbao, Robertson or Beidler, it would have gone against what the skilled artisan knew about cancer therapies. Namely, the skilled artisan would not believe that one would use an apoptotic inhibiting agent with a cancer therapy.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, and that such willful false statements may jeopardize the validity of the application or any patent that issues therefrom.

11/8/07

Date



David Waxman